Verastem Presents Data on Cancer Stem Cell-Targeting Agents at the 2014 AACR Annual Meeting

April 9, 2014

- Research Results Provide Additional Support for Targeting Cancer Stem Cells Directly and Through Immunomodulation of the Tumor Microenvironment –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 9, 2014-- Verastem, Inc. (NASDAQ:VSTM), focused on discovering and developing drugs to treat cancer by the targeted killing of cancer stem cells, today announced the presentation of scientific data at the American Association for Cancer Research annual meeting being held April 5 - 9, 2014, at the San Diego Convention Center in San Diego, CA.

"The data presented at AACR continue to expand our understanding of the mechanisms of our compounds targeting cancer stem cells," said Jonathan Pachter, Ph.D., Verastem Head of Research. "Of significant interest to us is that VS-6063 inhibits the focal adhesion kinase family members FAK and PYK2 which leads to the preferential targeting of cancer stem cells both directly and through inhibition of tumor-associated macrophages in the tumor microenvironment. This discovery is intriguing as published evidence in both mesothelioma and breast cancer has demonstrated a correlation between an increase in tumor-associated macrophages and poor prognosis in these patients."

Verastem is presenting these data in support of its programs targeting cancer stem cells through inhibition of the focal adhesion kinase (FAK; VS-6063 and VS-4718) and PI3K/mTOR (VS-5584) signaling pathways. Research on the FAK and PI3K/mTOR signaling pathways has revealed critical roles for each in cancer stem cell (CSC) survival and disease progression. CSCs represent a subpopulation of cancer cells that have tumor-initiating capability, are particularly resistant to chemotherapy and can mediate tumor recurrence both locally and at metastatic sites.

"These presentations continue to build upon a growing body of scientific evidence supporting the development of VS-6063, VS-4718 and VS-5584, which are potent inhibitors of cancer stem cells," said Robert Forrester, Verastem President and Chief Executive Officer. "Collectively, these data are helping elucidate the underlying mechanisms that are the foundation for our ongoing clinical programs. We are dedicated to advancing these novel treatments, working to extend therapeutic response and addressing the challenge that cancer stem cells represent for the effective treatment of cancer."

A summary of the data presented by Verastem at the conference is below:

Oral Presentation

Title: VS-6063 (defactinib) targets cancer stem cells directly and through inhibition of tumor-associated macrophages and cytokine production
Date and time: Tuesday, April 8, 2014, 4:20 pm – 4:35 pm PT
Location: Room 6B
Abstract Number: 4797
Session: Mini-symposium "Elucidation and Niche Targeting of Cancer Stem Cell Epigenetic and Metabolic Alterations"
Summary: Here we report that VS-6063 targets cancer stem cells directly and through an immunomodulatory effect by reducing tumor-associated macrophages. In addition to being a potent FAK inhibitor, study findings have demonstrated that VS-6063 also inhibits the activity of PYK2, a closely related protein kinase and only other member of the FAK family. Several lines of evidence suggest that dual targeting of FAK and PYK2 should confer greater antitumor efficacy than inhibition of either target alone. In PYK2 knockout mice, reduced macrophage infiltration has been observed. Tumor-associated macrophages (TAMs) have been correlated with poor prognosis in multiple cancer types, including mesothelioma and breast cancer. The effects of PYK2 inhibition on TAMs were investigated in the current study.

These research results demonstrated that VS-6063 directly kills CSCs through FAK inhibition. Interestingly, by inhibiting PYK2, VS-6063 also reduced the production of specific cytokines that are responsible for increasing cancer stem cells in mesothelioma and breast cancer in a dose dependent manner. A FAK-only reference inhibitor had no effect on these cytokines. Results also demonstrated that VS-6063 substantially reduced the number of TAMs in cancer xenograft models. The dual inhibition of FAK and PYK2 by VS-6063 effectively decreased CSCs directly, and both the presence of TAMs in tumors and the ability of TAMs to release cytokines that stimulate CSC proliferation and survival.

Poster Presentations

Title: Focal adhesion kinase (FAK) inhibitor VS-6063 (defactinib) preferentially targets cancer stem cells in triple negative breast cancer
Date and time: Tuesday, April 8, 2014, 1:00 pm – 5:00 pm PT
Location: Hall A-E
Abstract Number: 3908
Poster Section 2: Cancer Stem Cell Phenotype, Function, and Targeting
Summary: Here we report that VS-6063 potently targets, and abrogates chemotherapy-induced enrichment of, cancer stem cells in models of triple negative breast cancer. Triple negative breast cancer (TNBC) is characterized by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) gene expression, and comprises a heterogeneous group of breast cancers. Amplification and overexpression of FAK have been observed in aggressive human cancers, including breast cancer. In addition to regulating the proliferation, survival, invasion and metastasis of cancer cells, FAK also plays a critical role in the self-renewal and survival of CSCs. CSCs have been shown to be resistant to standard chemotherapy and associated with poor clinical outcomes.

These research results demonstrated that VS-6063 reduced the percentage of CSCs in human TNBC cells and reduced the proportion of CSCs in primary breast cancer tissue specimens cultured *ex vivo*. Standard of care agents (paclitaxel and doxorubicin) administered alone increased the percentage of CSCs suggesting these agents preferentially target bulk tumor cells. In contrast, when VS-6063 was administered in combination with

the standard of care agent paclitaxel, VS-6063 attenuated the enrichment of chemotherapy-induced CSCs. Oral administration of VS-6063 resulted in a reduction of tumor CSCs in a human TNBC xenograft model *in vivo*. Collectively, these results indicate that VS-6063 preferentially targets CSCs in TNBC and supports the clinical development of VS-6063 in combination with standard of care agents to achieve more durable responses through the simultaneous targeting of both CSCs and bulk tumor cells.

Title: Combined inhibition of PI3K isoforms and mTOR kinase is critical for cancer stem cell inhibition by VS-5584
Date and time: Tuesday, April 8, 2014, 1:00 pm – 5:00 pm PT
Location: Hall A-E
Abstract Number: 3906
Poster Section 2: Cancer Stem Cell Phenotype, Function, and Targeting
Summary: Here we report that pan-inhibition of both mTOR and the PI3K isoforms by VS-5584 is necessary for the effective targeting of cancer stem cells and that single isoform inhibition does not lead to a cancer stem cell preferential effect. VS-5584 is a highly potent dual inhibitor of mTORC1/2 and PI3K that preferentially targets CSCs *in vitro* and *in vivo*. VS-5584 has equipotency against all four human Class I PI3K isoforms and the mTOR kinase.

These research results demonstrated that VS-5584 decreased CSCs across multiple cancer cell lines, including TNBC cells, while paclitaxel increased the proportion of cancer stem cells. In small cell lung cancer models (H69), VS-5584 effectively eliminated the CSC population, with a corresponding substantial delay in tumor regrowth following cisplatin treatment. Similarly, ex vivo treatment with VS-5584 preferentially reduced CSCs in primary tumor specimens from patients with breast cancer or ovarian cancer. Interestingly, knock down of PI3Kα, PI3Kβ or mTOR alone was insufficient to decrease CSCs, while knock down of PI3Kα, PI3Kβ and mTOR together effectively reduced CSCs mimicking the effect of VS-5584. These data help to elucidate the mechanism of VS-5584 targeting of CSCs and provide a strong rationale for the clinical development of VS-5584 in combination with chemotherapeutic agents targeting bulk tumor cells to achieve more durable clinical responses in cancer patients.

Title: VS-5584 a dual mTORC1/2 and PI3K inhibitor has anti-tumor activity in multiple in vivo xenograft tumor models and enhanced efficacy in combination with cisplatin or docetaxel
Date and time: Sunday, April 6, 2014, 1:00 pm – 5:00 pm PT
Location: Hall A-E
Abstract Number: 213
Poster Section 8: Stem Cell Expansion and Cancer Stem Cell Targeting
Summary: Here we report that intermittent dosing of VS-5584 is comparable to daily dosing and has broad activity in models of multiple tumor types. In *in vitro* assays, VS-5584 has been shown to preferentially target CSCs and exhibited significant anti-proliferative activity across multiple cancer cell lines. Similarly, oral administration of VS-5584 has been shown to reduce CSCs in xenograft models. In this study, the *in vivo* anti-tumor efficacy of once daily and intermittent oral administration of VS-5584 was evaluated in several xenograft tumor models in small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), TNBC and mesothelioma.

These research results demonstrated that once daily treatment with VS-5584 resulted in potent and dose-dependent anti-tumor activity with mean percentage tumor growth inhibition (TGI) ranging from 40% to 97% ($P<0.05$), which was generally observed at well-tolerated dose levels. In evaluating intermittent dosing schedules, efficacy and tolerability were similar or better compared to continuous daily dosing. VS-5584 plus either cisplatin or docetaxel also showed a significant increase in TGI compared to cisplatin alone. The potent *in vivo* anti-tumor activity in xenograft models of SCLC, NSCLC, TNBC and mesothelioma suggests that VS-5584 has the potential for anticancer activity across a variety of cancer types. Importantly, intermittent dosing with VS-5584 was sufficient to achieve good efficacy while minimizing side effects, thus allowing a broader therapeutic window compared to daily dosing in these models.

About VS-6063

VS-6063 is an orally available compound designed to target cancer stem cells through the potent inhibition of focal adhesion kinase (FAK). Cancer stem cells are an underlying cause of tumor resistance to chemotherapy, recurrence and ultimate disease progression. Research by Robert Weinberg, Ph.D., scientific cofounder and chair of Verastem's Scientific Advisory Board, and Verastem has demonstrated that the FAK pathway is critical for the growth and survival of cancer stem cells. VS-6063 is currently being studied in the registration-directed COMMAND trial in mesothelioma (www.COMMANDmeso.com), a Phase 1/1b study in combination with paclitaxel for patients with ovarian cancer, a Phase 1 study in Japan in patients with advanced solid tumors and a Phase 2 trial in patients with Kras-mutated non-small cell lung cancer. VS-6063 has been granted orphan drug designation in the U.S. and E.U. for use in mesothelioma.

About VS-5584

VS-5584 is an orally available compound that has demonstrated potent and highly selective activity against class 1 PI3K enzymes and dual inhibitory actions against mTORC1 and mTORC2 pathways. In preclinical studies, VS-5584 has been shown to reduce the percentage of cancer stem cells and induce tumor regression in chemotherapy-resistant models. Verastem is currently conducting a Phase 1 dose escalation trial of VS-5584 in patients with advanced solid tumors and lymphomas.

About Verastem, Inc.

Verastem, Inc. (NASDAQ:VSTM) is discovering and developing drugs to treat cancer by the targeted killing of cancer stem cells. Cancer stem cells are an underlying cause of tumor recurrence and metastasis. Verastem is developing small molecule inhibitors of signaling pathways that are critical to cancer stem cell survival and proliferation: FAK, PI3K/mTOR and Wnt. For more information, please visit www.verastem.com.

Forward-looking statements:

This press release includes forward-looking statements about the Company's strategy, future plans and prospects, including statements regarding the development of the Company's compounds, the timeline for clinical development and regulatory approval of the Company's compounds, the expected timing for the reporting of data from ongoing trials, and the structure of the Company's planned or pending clinical trials, and potential indications for clinical development. The words "anticipate," "appear," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results

to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include the risks that the preclinical testing of the Company's compounds and preliminary data from clinical trials may not be predictive of the results or success of ongoing or later clinical trials, that data may not be available when we expect it to be, that the Company will be unable to successfully complete the clinical development of its compounds, that the development of the Company's compounds will take longer or cost more than planned, and that the Company's compounds will not receive regulatory approval or become commercially successful products. Other risks and uncertainties include those identified under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2013 and in any subsequent SEC filings. The forward-looking statements contained in this presentation reflect the Company's current views with respect to future events, and the Company does not undertake and specifically disclaims any obligation to update any forward-looking statements.

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